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09/036,614	03/07/1998	JENNIFER L. HILLMAN	#PF-0484US	6185

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Legal Department
Incyte Genomics, Inc.
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EXAMINER	
GUCKER, STEPHEN	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/036,614	Hillman et al.
Examiner	**Group Art Unit**
Stephen Gucker	1647

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 5/7/02.

☑ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 22-34 is/are pending in the application.

Of the above claim(s) 30-34 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 22-29 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Pat nt Application, PTO-152

☐ Other _____

Office Action Summary

R sponse to Amendment

1. Applicant's election with traverse of Group I, claims 22-29 in Paper No. 20, is acknowledged. The traversal is on the ground(s) that there is no search burden on the Examiner. This is not found persuasive because each sequence requires a search to be performed in the prior art and a separate updated search at the time of allowance in the interference databases of the USPTO that are doubling in size approximately every six months. Because the claims require the searching of a genus of at least 90% identity to each unique sequence, plus all encoded biologically active fragments, plus all encoded immunogenic fragments, and finally, all 20 and 60 nucleotide fragments, a search burden does indeed exist since Applicant is not simply claiming a single species of a single sequence.

Due to the increased database load and search burden for sequence searching the prior art, the PTO is currently restricting all nucleotide sequence applications to a single sequence. This is consistent with 1232 OG 242(116) where it was noted that "up to ten (10) independent and distinct nucleotide sequences will be examined...". Due to the exponential growth of the prior art sequence databases, the PTO has interpreted "up to ten" as including one nucleotide sequence.

The process claims covering the same scope as the product claims may be rejoined with the product claims upon allowance of the product claims.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 30-34 are withdrawn from further consideration by the examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

5. Claims 22-29 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a well-established utility or a disclosed specific and substantial credible utility. The asserted utility for encoding nucleic acid sequences for the kinesin light chain homolog (KILCH) is that mutations in kinesin cause severe disruption of axonal transport in larval nerves of the invertebrate fruit fly *Drosophila melanogaster* which leads to progressive paralysis and that this phenotype mimics the pathology of some vertebrate motor neuron diseases such as ALS (Lou Gerhig's Disease). However, the prior art of record relied on by the specification for this disclosed specific and substantial utility relates to mutations in the kinesin *heavy* chain (KHC) which is a separate and distinct protein from the kinesin *light* chain (KLC), let alone the instant invention, the kinesin light chain homolog (KILCH) which is a protein which shares some sequence identity (66%) with KLC, but is not KLC itself. Therefore, the Examiner does not find Applicant's evidence to be specific and substantial that KILCH is involved in pathologies like ALS because Applicant has relied on the prior art for an entirely different protein, KHC, to establish utility for KILCH. Although the protein kinesin is important in the intracellular transport of vesicles, the prior art of record is drawn to the importance and functionality of the KHC and relatively little is known about the importance and functionality of the KLC in comparison, and absolutely nothing is known about the pathological importance and/or functionality of the KILCH other than the prophetic teachings of the disclosure. KILCH has not been demonstrated by any data or sound scientific reasoning to possess any of the biological functions ascribed to it by the specification for its asserted utilities as a diagnostic or a therapeutic. The percentage sequence identity that KILCH shares with KLC is not persuasive to ascribe to KILCH the biological functions of KLC because a full third of the amino acids that make up the KILCH sequence are different than the KLC sequence. The disclosure teaches that KILCH and its encoding polynucleotides are useful in the diagnosis, treatment, and prevention of neurological, reproductive, and cell proliferative disorders. KILCH polynucleotide is expressed

in various libraries, at least 47% of which are associated with cancer and cell proliferation. However, many polynucleotides are expressed constituently in both normal control *and* cancer and cell proliferation libraries as ubiquitous sequences found in all cells, healthy or not. The fact that KILCH is found in some libraries associated with cancer and cell proliferation or other tissues does not mean that it can be used as a useful marker for such without forcing further research to be performed (analysis of frequency of false positives and false negatives, validity, predictability, etc.). Likewise, the use of encoding polynucleotides for KILCH as a therapeutic for the multitude of diseases listed in the specification is not credible because these diseases represent a multitude of different pathologies in their underlying or contributing causes, their varied symptomatology, and differing avenues of treatment. None of these boilerplate laundry-list of diseases have been shown to be associated in any way with the instant invention, either in the art of record or by a single scrap of scientific datum provided by Applicants. Other than being diseases of neurons or proliferation, the diseases listed do not have a single common unifying feature or mechanism underlying them that would lead the skilled artisan to believe that any single agent could treat all of them, least of all the agent of the instant invention that has no demonstrated function in normal healthy cells, let alone in diseased cells.

These aforementioned utilities are not considered to be specific and substantial because the specification fails to disclose sufficiently any particular function or biological significance for KILCH or its encoding nucleotides of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to one other known protein, KLC, which little is known about itself and which has no demonstrated or art accepted connection to any known specific disease or disorder. For instance, there are no known diseases or treatments of record that rely on the presence or absence of KLC (a known protein of the prior art), or that rely on KLC's proper functioning, whatever that function may be, in order for a physician to diagnose or treat any known condition. After further

research, a specific and substantial utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-tumor activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. §101, which requires that an invention must have either an immediately apparent or fully disclosed "real world" utility. The court held that:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field. . . . a patent is not a hunting license. . . .[i]t is not a reward for the search, but compensation for its successful conclusion.

The instant claims are drawn to encoding polynucleotides and their uses for a protein that, as yet, has undetermined function or biological significance. There is no evidence of record or any line of reasoning that would support a conclusion that the KILCH polynucleotides or uses thereof in the instant application were, as of the filing date, useful for diagnosis, prevention and treatment of cancer, neurological disease, or reproductive disorders, as stated in the specification. Until some actual and specific significance can be attributed to the protein identified in the specification as KILCH, or the gene encoding it, one of ordinary skill in the art would be

required to perform additional experimentation in order to determine how to use the claimed invention. Thus, there was no immediately apparent or "real world" utility as of the filing date.

Applicants' arguments filed 1/4/02 have been fully considered but they are not persuasive for reasons of record and the following. Applicants' mere assertion that the disclosed encoded polypeptide KILCH has biological activities similar to known kinesin family members is not credible in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen in vivo, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end of the article). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone

14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by only a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function; "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins" (see third sentence of abstract for the quotation, also see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multifunctionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. "Overpredictions are common because the highest-scoring database protein does not necessarily share the same or even similar functions" (Doerks et al., page 248). Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate

inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein, even if that small domain is in a non-functional region of the known protein (for example, assigning a new protein as being a functional enzyme based on matches to a known enzyme outside of the catalytic active site of the enzyme, even though the new protein lacks the known catalytic domain! This would be like assuming football fans in a stadium function at the athletic level of professional football players because their jerseys "match" the jerseys of the players on the field). Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted specific and substantial utility of putative kinesin light chain activity because the encoded KILCH polypeptides have never been actually produced and tested for any actual biological function. The only basis the disclosure has for asserting that the instant invention encodes for a protein that potentially possesses kinesin light chain functionality (whatever that might be) is based on a weak sequence similarity (only 66% between KILCH and human kinesin light chain (KLC)) while, in comparison, human and rat KLC share 98% sequence identity. All of the aforementioned scientific documents discussed here casts serious

doubt on Applicant's approach to ascribe to an unknown protein or the polynucleotides that encode it (that share only 66% sequence identity to a known protein of unknown specific function) a specific functionality to this protein that has never been actually produced or expressed from its encoding nucleotides. In fact, as some of the prior art discussed here shows, an encoded protein's functionality may be the exact opposite of what was predicted from its sequence similarities to known proteins and that such determinations of biological significance or functionality can only be seen when the encoded protein is actually made, which was not done in the instant disclosure.

The specification does not support a specific and substantial utility regarding the claimed polynucleotides encoding KILCH and variants thereof for purposes unrelated to the asserted biological activity. For example, the specification asserts that the claimed polynucleotides are involved in cell proliferative, neurological, and reproductive disorders based solely on the structural similarity between human KILCH and human KLC. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides. Neither does any of the prior art of record. Also, the specification does not predict whether the claimed polynucleotides would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control. The specification contains assertions that the claimed polynucleotides can be used in gene expression monitoring assays, which are used in the art for drug development studies. However, without a disclosure of a particular disease state in which the claimed polynucleotides are expressed at an altered level or form, it would be impossible to determine what the results of a gene expression monitoring assay mean. For example, if a compound is tested on a microarray comprising the claimed

polynucleotides and affects expression of the polynucleotides negatively, it cannot be determined if that means that the compound is a potentially good drug for a disease or would exacerbate the disease if administered. The test results also would not have meaning in terms of what specific disease is relevant. The asserted utility in gene expression monitoring assays is thus not substantial, because significant further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are overexpressed or underexpressed in the diseased tissue. Furthermore, since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitute a specific and substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ at 696.

Applicant's argue that there is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. This is inaccurate for the reasons previously discussed. Without having some basic knowledge or nexus between the instant polynucleotides and some specific disease state, whether an increase or decrease in expression is a desirable or undesirable outcome, and how a physician would specifically and substantially use that information for either diagnostic, prognostic, or therapeutic purposes, the usefulness of the gene expression analysis is in dispute. In other words, to ask a "real-world"

utility question, what action would my physician prescribe for me to take if upon gene expression analysis, my KILCH polynucleotides increased by 40% when I stopped taking testosterone (a hormone that can be used as a drug) to treat male infertility (a reproductive disorder)? The teachings of the specification cannot answer this, or any other medical question concerning a single disease state, regardless of whether that question concerns prophylaxsis, treatment, or diagnosis of even a single specific disease. The Applicant cannot point to a single teaching in the specification where a specific increase or decrease in KILCH polynucleotides would lead the artisan to a single specific conclusion as to what the biological significance of that finding would mean in a single specific disease state, and thus the invention lacks specific and substantial utility as being an invention only useful for further research.

Applicant's arguments concerning toxicology testing are unpersuasive because the instant specification does not mention toxiciology testing as a utility for the instant KILCH polynucleotides. In addition, as with drug testing, the significance of increases or decreases in KILCH polynucleotides in regards to toxicology cannot be ascertained because there is no teachings in the specification as to whether increases or decreases in KILCH polynucleotides are indicative of any particular drug or toxin, or whether an increase or decrease in expression of KILCH polynucleotides is a desirable or undesirable outcome in response to any toxin or drug so tested.

For example, if a compound is tested on a microarray comprising the claimed polynucleotides and affects expression of the polynucleotides negatively, it cannot be determined if that means that the compound is a potential good drug for a disease or would exacerbate the disease if administered. The test results also would not have meaning in terms of what specific

disease is relevant. The asserted utility in gene expression monitoring assays is thus not substantial, because significant further research would have to be conducted to determine which diseases correlate with altered forms or levels of the claimed polynucleotides, and whether the claimed polynucleotides are overexpressed or underexpressed in the diseased tissue. Furthermore, since any expressed polynucleotide can be added to a microarray for gene expression monitoring, the asserted utility is not specific to the claimed polynucleotides.

Applicant characterizes the invention as a polynucleotide sequence corresponding to a gene that is expressed in human tissues and that codes for a polypeptide which is a member of the class of kinesin homologs having biological functions including involvement in cell proliferation. Based on this, Applicant urges that the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development and diagnosis of disease, none of which requires knowledge of how the polypeptide coded for by the claimed polynucleotide actually functions. Applicant states that the claimed invention already enjoys significant commercial success. This has been fully considered but is not found to be persuasive for several reasons. The specification does not disclose that the claimed genes are markers for specific diseases. Absent a disclosure of altered levels or forms of a gene in diseased tissue as compared with the corresponding healthy tissue, the gene is not a disease marker or an appropriate target for drug discovery or toxicology testing. Finally, evidence of commercial success, while sometimes persuasive as secondary evidence of non-obviousness, is immaterial to utility and enablement. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility and enablement.

Applicant discusses the Bedilion declaration submitted with the amendment filed 1/4/02. Applicant characterizes the Bedilion declaration as describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications, thus allegedly demonstrating the examiner's position to be without merit. In particular, Applicant states that the Bedilion declaration describes how the claimed expressed polynucleotide can be used in gene expression monitoring systems that were well-known at the time of the invention, and how those applications are useful in developing drugs and monitoring their activity. Applicant quotes from the Bedilion declaration, that states that microarrays containing SEQ ID NO: 1-encoding and SEQ ID NO: 2 would be a more useful tool than microarrays lacking same in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative and developmental disorders for such purposes as evaluating their efficacy and toxicity. This is not found to be persuasive. As an aside, it is noted that Dr. Bedilion is a consultant for Incyte Pharmaceuticals, Inc., the real party in interest in this appeal, and thus is a concerned party. Regarding the merit of the argument, any new polynucleotide can be used in a microarray, and thus this asserted utility is not specific. Also, the disclosure that KILCH is structurally related to KLC gene does render the asserted utility specific, since the specification does not establish that either KILCH or KLC is expressed in any diseased tissues in any way that is different from the way it is expressed in healthy forms of the same tissues. In other words, the specification does not disclose that KILCH or KLC is expressed in tissues having cell proliferative or developmental disorders at altered levels or forms. Thus, it is not a target for drug development, toxicology studies, or disease diagnosis. Significant further research would

have to be conducted to identify diseases states which correlate with altered levels or forms of the claimed polynucleotides. Therefore, this asserted utility is also not substantial.

Applicant criticizes the examiner's position that the claimed polynucleotide cannot be useful without precise knowledge of its biological function. However, Applicant is mischaracterizing the examiner's position. A specification can meet the legal requirements of utility and enablement for a new polynucleotide as long as the specification discloses a specific and substantial asserted utility for the new polynucleotide, or a well-established utility for the claimed polynucleotide. A hypothetical example may serve to clarify. For example, a hypothetical specification discloses that a claimed polynucleotide is expressed in colon cancer and not expressed in healthy colon tissue. The hypothetical specification does not disclose the biological activity of the polypeptide encoded by the polynucleotide. The claimed polynucleotide in the hypothetical example would not be rejected under 35 U.S.C. §§ 101 and 112, first paragraph, as it has utility and is enabled as a colon cancer marker. However, such is not the fact pattern here. The instant specification discloses that the claimed polynucleotides are structurally related to KLC and hypothesizes that the claimed polynucleotides are involved in cell proliferative and developmental disorders, but the expression of the KILCH polynucleotide in diseased tissues and the corresponding healthy tissues was not evaluated. Therefore, there is no disclosure that the claimed polynucleotides are expressed at altered levels or forms in any specific, diseased tissue. It is noted that the instant application was filed 06 March 1998. No evidence has been brought forth during the prosecution history regarding the expression levels in diseased or healthy tissue. Also, no evidence has been brought forth that the claimed polynucleotides encode polypeptides having specific KLC activities.

Applicant argues that the use of KLC polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer specific benefits to the public. Applicant states that there is no dispute that the claimed invention is a useful tool in cDNA microarrays used to perform gene expression analysis. Applicant asserts that such is sufficient to establish utility for the claimed polynucleotide. This is not found to be persuasive. While the examiner agrees that any polynucleotide, including the claimed polynucleotides, can be used in a cDNA microarray, such does not confer patentable utility on the claimed polynucleotides. Since any polynucleotide can be used in a microarray, such a use is not specific to the claimed polynucleotides. Just as any orphan receptor can be used in an assay to screen for ligands, such does not confer patentable utility on a particular orphan receptor. Such can be done with any orphan receptor, and thus the asserted utility is not specific. Furthermore, since the specification does not disclose a correlation between any disease or disorder and an altered level or form of the claimed polynucleotides, the results of gene expression monitoring assays would be meaningless without significant further research. Therefore, the asserted utility is also not substantial.

Applicant refers to the Bedilion declaration as explaining the many reasons why a person skilled in the art reading the instant application would have understood that application to disclose the claimed polynucleotide to be useful for a number of gene expression monitoring applications, such as a probe for expression of the polynucleotide in connection with the development of drugs and the monitoring of the activity of such drugs. The Bedilion declaration discusses microarrays and Northern analysis for measuring such. Specifically, Applicant quotes from the Bedilion declaration that a person skilled in the art would have been able to use the

claimed polynucleotide in gene expression monitoring to develop new drugs for the treatment of cell proliferative and developmental. This is not found to be persuasive. The instant specification does not substantiate a link between the claimed polynucleotides and any specific cell proliferative or developmental disorder. The specification merely discloses that the claimed polynucleotides are structurally related to growth factors, and that they are expected to be involved in cell proliferative and developmental processes (and thus, disorders). The specification does not disclose the results of the required control in order to draw any conclusions regarding disease, namely, that the claimed polynucleotide is not expressed (or is expressed at an altered level or form) in the corresponding healthy tissues. Many genes expressed in diseased tissues have nothing whatsoever to do with the disease and are not targets for drug development or toxicology. For example, actin and histone genes are expressed in diseased tissues; they are constitutively expressed in all tissues. These are not suitable targets for drug development or toxicology studies, since disruption of these genes would kill the patient. Applicant refers to the opinion of Dr. Bedilion that a person skilled in the art at the time of the invention would have concluded that a cDNA microarray containing the claimed polynucleotide would be a more useful tool than a microarray lacking the claimed polynucleotide in connection with conducting gene expression monitoring studies on proposed or actual drugs for treating cell proliferative or developmental disorders for such purposes as evaluating the efficacy and toxicity. Again, this is not found to be persuasive, because the instant specification has not established that the claimed polynucleotides are expressed at altered levels or forms in diseased tissue as compared with the corresponding healthy tissue. If the claimed polynucleotide were in a microarray and a compound caused decreased expression of the claimed polynucleotide, what

would that mean to the skilled artisan? Is it a potential drug, or would administering the compound be likely to exacerbate the disease? If it had been disclosed that the claimed polynucleotide is expressed at a higher level in a particular cell proliferative diseased tissue as compared with the corresponding healthy tissue, then the skilled artisan would know that a compound that decreased expression of the polynucleotide is a good potential cell proliferative disease drug. However, that is not disclosed by the instant specification. The claimed polynucleotides may very well be expressed at equivalent levels in healthy tissues. If that is the case, then the compound would not be a good potential drug. The claimed polynucleotides may also very well be expressed at a lower level in a particular cell proliferative diseased tissue as compared to the corresponding healthy tissue. Then a compound that decreased expression of the claimed polynucleotides would not be a good potential drug. Evidence of a differential expression might serve as a basis for use of the claimed polynucleotide as a diagnostic for a disease. However, in the absence of any disclosed relationship between the claimed polynucleotide or the protein that is encoded thereby and any disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Applicant discusses the Bedilion declaration's detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations. Applicant points to Dr. Bedilion's pages of text and numerous subparts explaining the importance of this

technology. Applicant points to Dr. Bedilion's explanation that those skilled in the art at the time of the invention without any doubt would have appreciated the criticality of toxicity testing. This is not found to be persuasive. There is no doubt that cDNA microarray technology is an extremely valuable technique in gene expression monitoring, toxicology testing, and drug efficacy testing. However, the claims are not drawn to the technique. The claims are directed to polynucleotides which have not been disclosed as being associated with any particular disease or condition by its being expressed at an altered level or form in diseased tissue as compared to the corresponding healthy tissue. Any such polynucleotide could be added to a microarray. Thus, this asserted utility is not specific. Determining the relationship between the claimed polynucleotides and any specific disease or disorder would require significant further research. Therefore, this asserted utility is also not substantial.

Applicant urges that the Bedilion declaration establishes that persons skilled in the art, guided by the instant specification, at the time of the invention would have wanted their cDNA microarrays to comprise the claimed polynucleotide, because a microarray comprising the claimed polynucleotide would provide more useful results in the kind of gene expression monitoring studies that microarrays lacking the claimed polynucleotide. This is not found to be persuasive. The specification has not linked the claimed polynucleotide with any specific disease state or disorder, as discussed above and in previous Office Actions. Adding the claimed polynucleotide to a microarray would not make the microarray any more valuable than adding any other "orphan" polynucleotide. The asserted utility is not specific to the claimed polynucleotide.

Applicant argues that the examiner does not address the fact that, as described in the specification, the claimed polynucleotide can be used as highly specific probes to measure both the existence and amount of complementary mRNA sequences known to be expression products of the claimed polynucleotides. Applicant concludes that the claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine. This is not found to be persuasive. Any polynucleotide is a highly specific probe for itself or its complement, or any mRNA that can be transcribed from it. Such can be said for any polynucleotide. Thus, this asserted utility is not specific.

Applicant argues that, given that the claimed polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. Applicant reviews case law pertinent to the patentable utility of research tools. This is not found to be persuasive. Applicant's analogy is misplaced. It is true that a scale has patentable utility as a research tool. However, the object being weighed on the scale does not necessarily have patentable utility. In the instant case, microarray technology has patentable utility. However, the microarray is not being claimed, but rather a polynucleotide that can be used in microarrays. The claimed polynucleotide is not disclosed as being expressed at an altered level or form in any diseased tissue as compared to the corresponding healthy tissue. Therefore, the assertion that the claimed polynucleotide has patentable utility as a probe in, or member of, a microarray is not specific. Any orphan polynucleotide can be used in the same way.

Applicant argues that there can be no reasonable dispute that persons skilled in the art have numerous uses for information about relative gene expression including understanding the

effects of a potential drug for treating cell proliferative and developmental disorders. Applicant urges that, since the specification discloses the claimed polynucleotide to be expressed in cancer and immortalized cell lines, and the fact that the claimed polynucleotide is structurally related to other growth factors known to be associated with cell proliferative and developmental diseases, the skilled artisan would have derived more information about a potential cell proliferative and developmental disorder drug candidate or potential toxin with the claimed invention than without it. Again, this is not found to be persuasive, because the specification does not disclose that the claimed polynucleotide is expressed at an altered level or form in any particular disease or disorder as compared to the corresponding healthy tissues. It may be useful to consider how broad the term "cell proliferative disorders or developmental disorders" is. Cell proliferative disorders include cancers, psoriasis, warts and slow-closing wounds. Developmental disorders can affect any tissue at any time in its development. Even if it could be assumed that the claimed polynucleotides play a role in a cell proliferative or developmental disorder, determining which disorders are involved and how the claimed polynucleotides are altered during the disorder requires significant further research.

Applicant refers to Dr. Bedilion's discussion of the Brown et al. Patent (U.S. 5807522), attached to the declaration. Dr. Bedilion characterizes the patent as providing evidence that microarrays can be used in numerous genetic applications, including monitoring of gene expression in different tissue types, disease states, in response to drugs, and in response to potential toxins. This is not found to be persuasive. The Brown patent claims methods of forming microarrays. Microarray methods have patentable utility as a research tool, just like a scale or a gas chromatograph. However, what the research tool measures does not necessarily

have patentable utility, such as the object being weighed by the scale, or the compound being analyzed by the gas chromatograph. Such is the situation at issue.

Applicant refers to other publications that discuss microarrays and gene expression technology with respect to drug screening and toxicology. Again, this is not found to be persuasive, because the arguments and evidence merely show that microarray technology is important and useful to the scientific community. These publications do not show that the claimed invention has a patentable utility. The use of the claimed uncharacterized polynucleotides in such studies would have provided no more information than the use of any other orphan polynucleotide. The asserted utility for the claimed polynucleotide is not specific to the claimed polynucleotide. Due to the lack of disclosure of a correlation between the claimed polynucleotides and a particular disorder, the asserted utility is also not substantial, as discussed above.

Applicant argues that the claimed polynucleotides are useful as tools for toxicology testing, drug discovery, and the diagnosis of disease and that these uses are "well-established". Each of these uses will be addressed individually, because the facts and issues directed to each use are distinct and separable. First, Applicant argues that toxicology testing is a well-established utility and concludes that the claimed polynucleotides could be used in this manner and that the claimed invention possesses utility. However, for a utility to be "well-established" it must be specific and substantial. In this case, all nucleic acids and genes are in some combination useful in toxicology testing. However, the particulars of toxicology testing with the claimed polynucleotides are not disclosed in the instant specification. Neither the toxic substances nor the susceptible organ systems are identified. Therefore, this is a utility which

would apply to virtually every member of a general class of materials, such as any collection of proteins or DNA, but is only potential with respect to the claimed polynucleotides. Because of this, such a utility is not specific and does not constitute a "well-established" utility. Further, because any potential diagnostic utility is not yet known and has not yet been disclosed, the utility is not substantial because it is not currently available in practical form. Moreover, use of the claimed polynucleotide in an array for toxicology screening is only useful in the sense that the information that is gained from the array is dependent on the pattern derived from the array, and says nothing with regard to each individual member of the array. Again, this is a utility which would apply to virtually ever member of a general class of materials, such as any collection of proteins or DNA. Even if the expression of Applicant's individual polynucleotides are affected by a test compound in an array for drug screening, the specification does not disclose any specific and substantial interpretation for the result, and none is known in the art. Given this consideration, the individually claimed polynucleotides have no "well-established" use. The artisan is required to perform further experimentation on the claimed material itself in order to determine to what "use" any expression information regarding this nucleic acid could be put.

With regard to drug discovery and development, Applicant mentions expression profiling as one use of the claimed polynucleotide. Applicant refers to recent developments as providing evidence that the benefits of this information are already beginning to manifest themselves. However, Applicant is incorrect in asserting that the efficacy (ability of producing a desired effect) of a compound could be evaluated from the result of a transcript image because there is no way to assess the meaning of any individual hit obtained from this procedure. The first

requirement is that one must know the biological significance of the polynucleotide(s) which is(are) being evaluated. Without this information, the results of the transcript image are useless because one would not know if the polynucleotide expression should be increased or decreased or even what significance could be attributed to such changes in expression profiles.

With regard to diagnosis of disease, in order for a polynucleotide to be useful, as asserted, for diagnosis of a disease, there must be a well-established or disclosed correlation or relationship between the claimed polynucleotide and a disease or disorder. The presence of a polynucleotide in tissue that is derived from cancer cells is not sufficient for establishing a utility in diagnosis of disease in the absence of some information regarding a correlative or causal relationship between the expression of the claimed cDNA and the disease. If a molecule is to be used as a surrogate for a disease state, some disease state must be identified in some way with the molecule. There must be some expression pattern that would allow the claimed polynucleotide to be used in a diagnostic manner. Many proteins are expressed in normal tissues and diseased tissues. Therefore, one needs to know, e.g., that the claimed polynucleotide is either present only in cancer tissue to the exclusion of normal tissue or is expressed in higher levels in diseased tissue compared to normal tissue (i.e. overexpression). Evidence of a differential expression might serve as a basis for use of the claimed polynucleotides as diagnostics for diseases. However, in the absence of any disclosed relationship between the claimed polynucleotides or the proteins that are encoded thereby and any disease or disorder and the lack of any correlation between the claimed polynucleotides or the encoded proteins with any known disease or disorder, any information obtained from an expression profile would only serve as the basis for further research on the observation itself. "Congress intended that no

patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." Brenner v. Manson, 148 USPQ at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. §101.

Applicant argues that the utility of the claimed polynucleotide can be imputed based on the relationship between KILCH and kinesin. Applicant urges that the examiner must accept that the homology demonstrates utility unless evidence or sound scientific reasoning is brought forth that a person of ordinary skill in the art would doubt utility. The argument is not found to be persuasive, because evidence that a person of ordinary skill in the art would doubt utility in this case has been brought forth. To clarify, the examiner never asserted KILCH is unrelated to KLC or kinesin. They are clearly structurally related. However, the rejection sets forth that, among related polypeptides in protein families, structural similarity is not predictive of functional similarity. For example, Vukicevic et al. (1996, PNAS USA 93:9021-9026) was cited in this response to Applicant's arguments as disclosing that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions. OP-1 and BMP-2 are approximately 60% identical. It is noted that OP-1, BMP-2 and GDF-9 are all TGF-β family members. Kopchick et al. (U.S. Patent 5,350,836) was cited as disclosing several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid. These pairs of polypeptides are 99.5% identical. Therefore, whereas it is credible that KILCH is related to KLC, the relationship is structural. Functional relatedness is not supported in the face of evidence in the art that structurally related polypeptides in protein families are frequently dissimilar functionally.

a showing of commercial success or actual use. As argued previously, many products which lack patentable utility enjoy commercial success, are actually used, and are considered valuable. These include silly fads such as pet rocks, but also include serious scientific products like orphan receptors.

Applicant asserts that the examiner improperly refused to impute the utility of kinesin homolog family to the claimed invention. Applicant urges that the case law requires only that the class not contain a substantial number of useless members. Applicant urges that the examiner has treated KILCH as if it were in the general class of all polynucleotides, rather than the kinesin homolog class. Applicant concludes that the examiner has not presented any evidence that the kinesin homolog class of proteins has any, let alone a substantial number, of useless members. This is not found to be persuasive. The kinesin family is functionally highly diverse, as evidenced by the references made of record in the rejection to the differences between KHC and KLC. When there is great functional diversity in a structurally related class of compounds, the class cannot be used to predict a utility for a new compound that fits in the class by structural similarity. Such is the case here.

Applicant argues that the kinesin homolog family is known to modulate cell proliferation, and the person of ordinary skill in the art need not know anything more about the claimed invention in order to be able to use it. Applicant urges that knowledge that KILCH is a KLC homologs is more than sufficient to make it useful for the diagnosis and treatment of cell proliferative and developmental disorders. Applicant states that KLC has been shown to be expressed in cancer cells. Applicant concludes that these facts must be accepted as true in the

absence of evidence or sound scientific reasoning to the contrary. This is also not found to be persuasive. While it is true that most growth factors and hormones affect cell proliferation, there is a great diversity of cell types affected by these polypeptides. The specification does not disclose which cell types are responsive to the polypeptides encoded by the claimed polynucleotides. Significant further research would be required of the skilled artisan to determine which cells are responsive, and thus the asserted utility is not substantial. Similarly, mere expression in a cancer cell does not mean that the polynucleotide is an appropriate target for drug development or toxicology testing. Cancer cells express many polynucleotides, such as constitutively expressed polynucleotides, which are not appropriate targets. The specification has not disclosed a specific disease or disorder of any type wherein the claimed polynucleotides are expressed at altered amounts or forms relative to the required control healthy tissue. Significant further research would be required of the skilled artisan to identify such a disease or disorder. Therefore the asserted utility is not substantial.

5. No claim is allowed.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (703) 308-6571. The examiner can normally be reached on Monday to Friday from 0930 to 1800. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is currently (703) 308-4242, but Applicant should confirm this by phoning the Examiner before faxing.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SG

Stephen Gucker

3/10/03

Gary L. Kunz

GARY KUNZ
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600